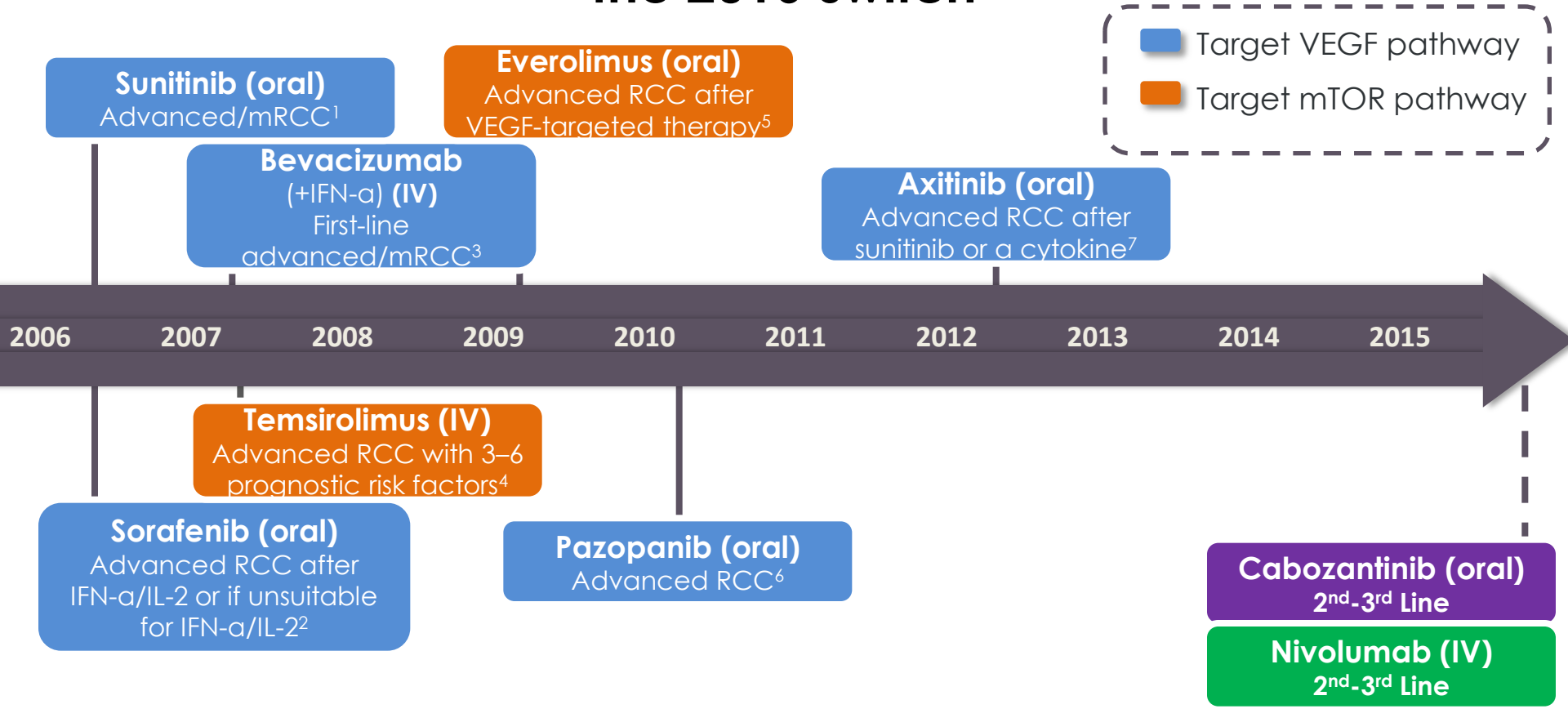
2nd Line Real World Data for IO in RCC

Laurence Albiges
Gustave Roussy Institute

CKCF19, Toronto April 12th

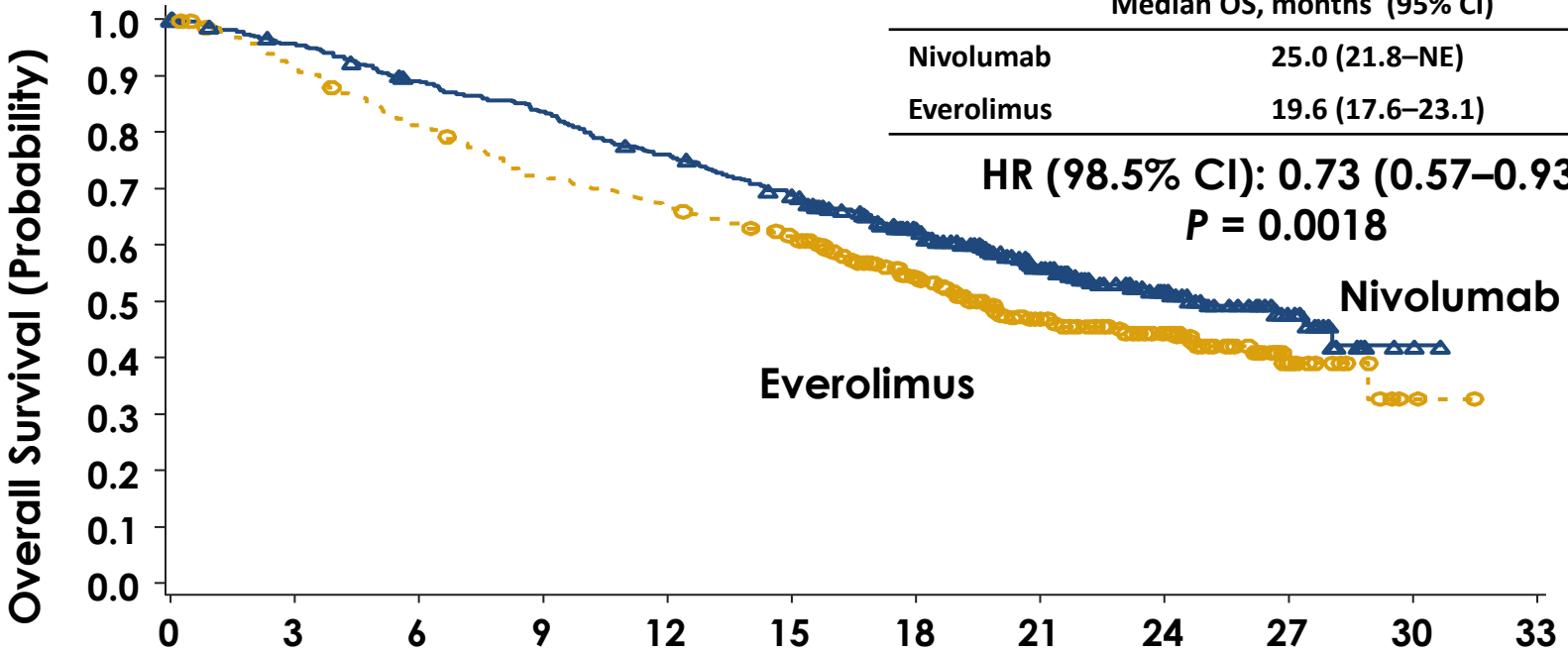
Targeted agents currently approved for mRCCc the 2016 switch



Ann Oncol. 2019 Feb 21. **Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.**
Escudier B[1], Porta C[2,3], Schmidinger M[4], Rioux-Leclercq N[5], Bex A[6,7], Khoo V[8,9], Grünwald V[10], Gillessen S[11,12], Horwich A[13]; ESMO Guidelines Committee.

Eur Urol. 2019 Feb 22.
European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update.
Ljungberg B[1], Albiges L[2], Abu-Ghanem Y[3], Bensalah K[4], Dabestani S[5], Montes SF[6], Giles RH[7], Hofmann F[8], Hora M[9], Kuczyk MA[10], Kuusk T[11], Lam TB[12], Marconi L[13], Merseburger AS[14], Powles T[15], Staehler M[16], Tahbaz R[17], Volpe A[18], Bex A[19].

Overall survival



Median OS, months (95% CI)	
Nivolumab	25.0 (21.8–NE)
Everolimus	19.6 (17.6–23.1)

HR (98.5% CI): 0.73 (0.57–0.93)
***P* = 0.0018**

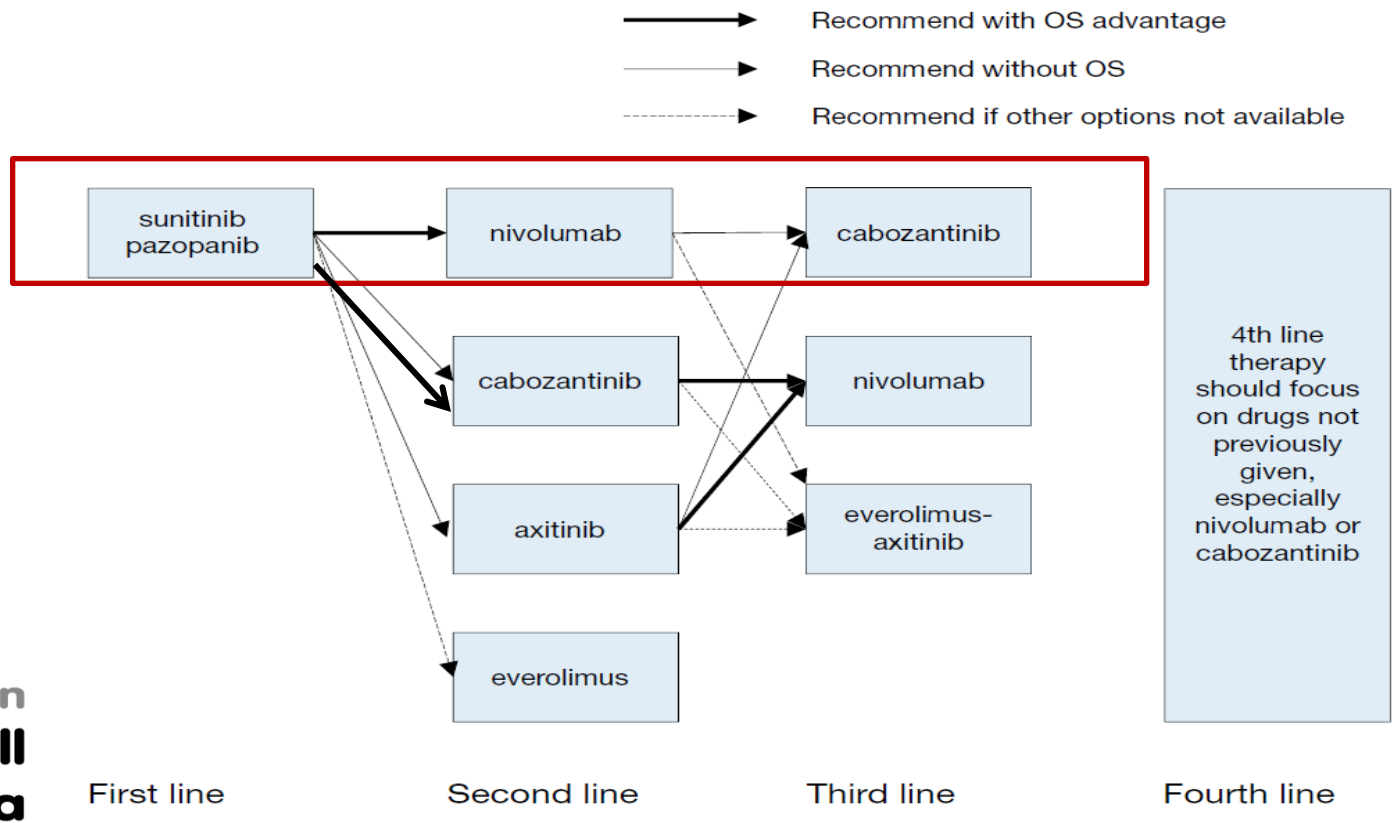
No. of patients at risk												
Nivolumab	410	366	359	337	305	275	213	139	73	29	3	0
Everolimus	411	389	324	287	265	241	187	115	61	20	2	0

Minimum follow-up was 14 months.
NE, not estimable.

Motzer et al. NEJM 2015

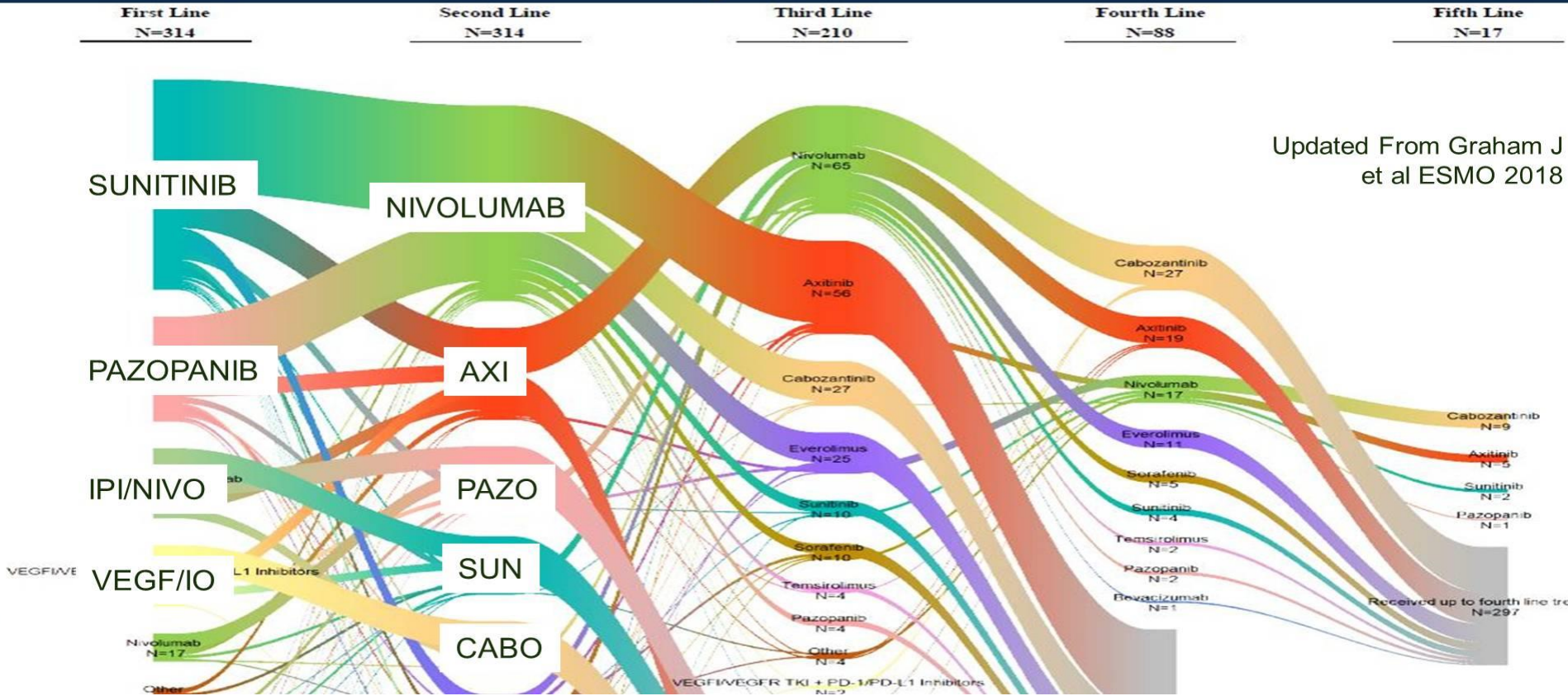
2016 EAU Guidelines

Figure 7.1: Recommendations for patients with metastatic clear cell-RCC who have failed one or more lines of VEGF targeted therapy



EAU Guidelines on
Renal Cell Carcinoma

Real World IO Sequences

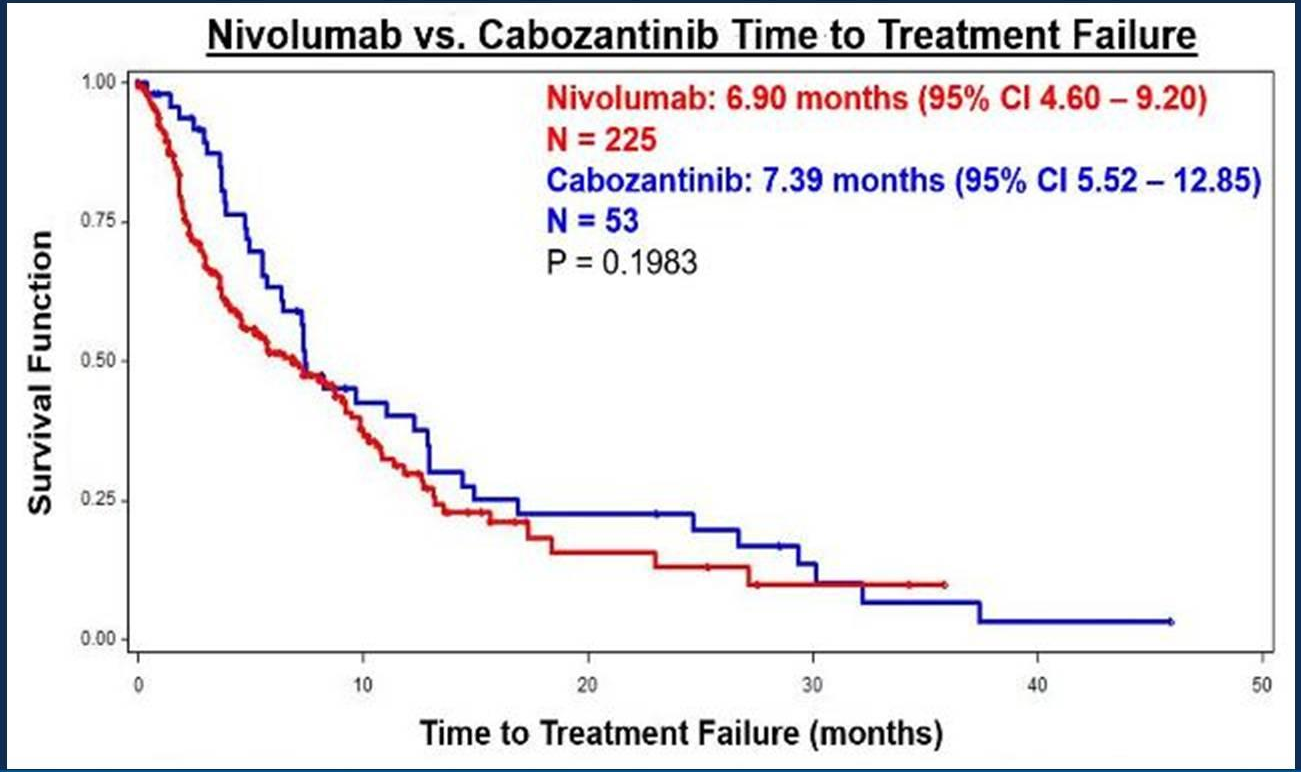


Presented By Daniel Heng at 2019 Genitourinary Cancers Symposium

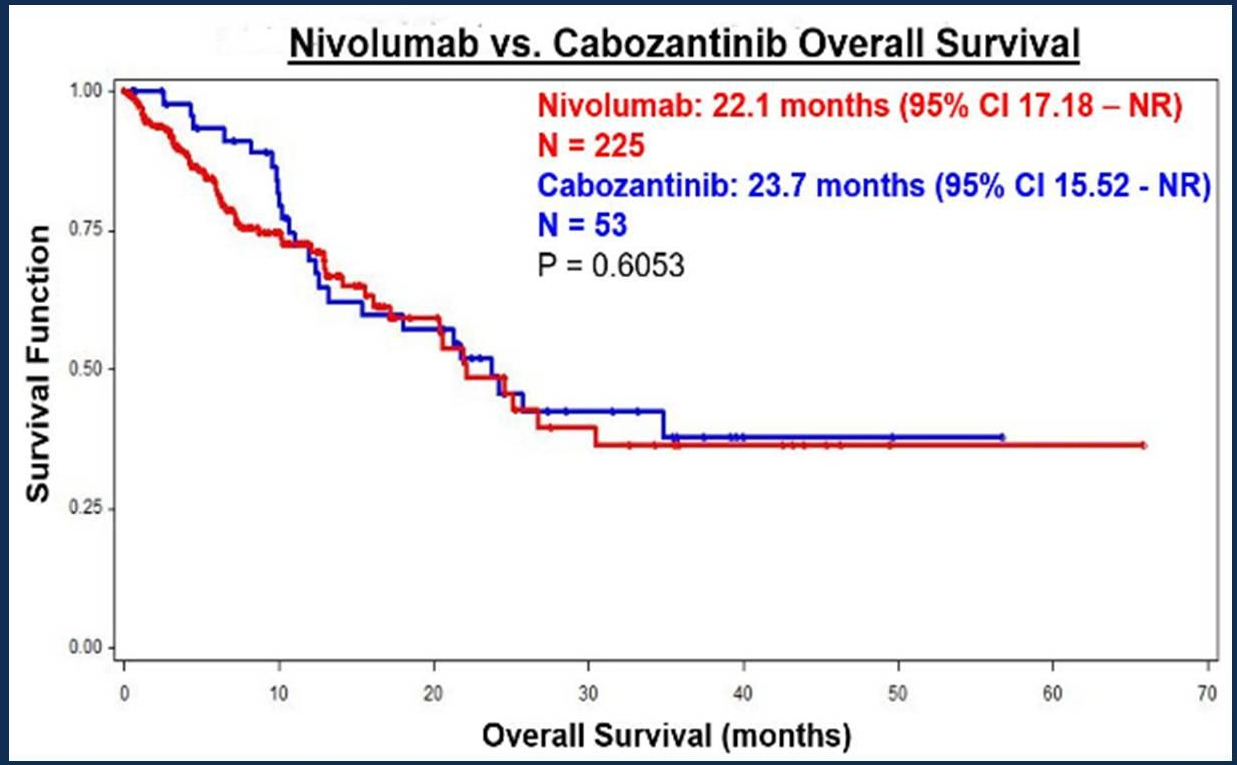
Post VEGF TKI
IMDC: 2nd line Cabozantinib vs Nivolumab

	Cabozantinib N= 53		Nivolumab N=225	
IMDC Risk Category (p=0.8766)				
Favorable Risk	6/39	(15%)	21/157	(13%)
Intermediate Risk	27/39	(69%)	107/157	(68%)
Poor Risk	6/39	(15%)	29/157	(19%)
Best Response:				
CR	1/40	(3%)	2/140	(1%)
PR	7/40	(18%)	28/140	(20%)
SD	23/40	(58%)	48/140	(34%)
PD	9/40	(23%)	62/140	(44%)
ORR	**8/40**	**(20%)**	**30/140**	**(21%)**

Post VEGF TKI
IMDC: 2nd line Cabozantinib vs Nivolumab



Post VEGF TKI
IMDC: 2nd line Cabozantinib vs Nivolumab



Final analysis from the NIVOREN GETUG AFU 26 study

L. Albiges, S. Negrier, C. Dalban, C. Chevreau, G. Gravis, S. Oudard, B. Laguerre, P. Barthelemy, D. Borchiellini, M. Gross-Goupil, L. Geoffrois, F. Rolland, A. Thiery-Vuillemin, F. Joly, S. Ladoire, F. Tantot, B. Escudier

on bealf of the GETUG

GETUG AFU 26 - NIVOREN (NCT03013335)

- Study objective: to evaluate safety and efficacy of Nivolumab in a “real world setting”

- Study design:
  - Prospective
  - Single arm
  - French multicenter

- Treatment:
  - Nivolumab 3mg/kg Q2W

Study design: Inclusion criteria

- mRCC with clear cell component
- Failed at least 1 line of VEGF/VEGFR inhibition

Inclusion criteria allowed:

- PS 0-2
- > 2 prior lines
- prior mTOR inhibitor
- asymptomatic brain metastases (BM)
- impaired renal function (Cl>40mml/min)

Patients disposition

720 patients enrolled from 01/ 2016 to 07/2017 across 26 centers in France

Median Follow up (Kaplan-Meier reverse) : 23.9 months $CI_{95\%}$[23.0;24.6]

	N=720
Treatment discontinuation, %	642 (89.2%)
Reasons for treatment discontinuation, %	
Disease progression	434 (60.3%)
Averse event/toxicity	101 (14.0%)
Patient/physician's choice	52 (7.2%)
Death	40(5.6%)
Other	15(2.1%)
Median duration of therapy (range), months	5.2
Median doses received (range), no	11(1;70)

Baseline characteristics

Characteristics		N = 720
Median age (range), years		64 (22;90)
Male, %		556 (77.2%)
ECOG Performance Status (PS)	0 1 2	229 (33.5%) 352 (51.5%) 103 (15.1%)
IMDC prognostic group, %	Favorable (0) Intermediate (1–2) Poor (3–6)	131 (18.2%) 404 (56.3%) 183 (25.5%)
Nephrectomy		609 (84.6%)
Number of prior systemic line	1 2 3 ≥4	359 (49.9%) 199 (27.6%) 96 (13.3%) 66 (9.1%)

Characteristics		N = 720
Brain metastasis	Yes	83 (12.3%)
Prior Everolimus	Yes	154 (21.4%)
GFR (ml/min)	≥60 <60 unknown	445 (63.3%) 258 (36.7%) 17
Nature of prior therapy (Overall)	Sunitinib Pazopanib Axitinib Everolimus Sorafenib Bevacizumab Cytokines temsirolimus Others	600 (83.3%) 178 (24.7%) 195 (27.1%) 154 (21.4%) 45 (6.3%) 39 (5.4%) 24 (3.3%) 20 (2.8%) 33 (4.6%)

Primary endpoint: Safety

	N=720
Grade 3-5 adverse event (AE),%	457 (63.5%)
Treatment-related adverse event(TRAE) grade 3-4, %	**129 (17.9%)**
Treatment-related deaths, n	6*
TRAE (any grade) leading to treatment discontinuation, %	64 (8.9%)
TRAE (grade≥3) requiring treatment, %	90 (12.5%)

*2 Cardiac failure, 1 pneumonia, 1 macrophage activation syndrome, 1 unknown cause, 1 cerebral hemorrhage

Safety - Grade 3-5 TRAES

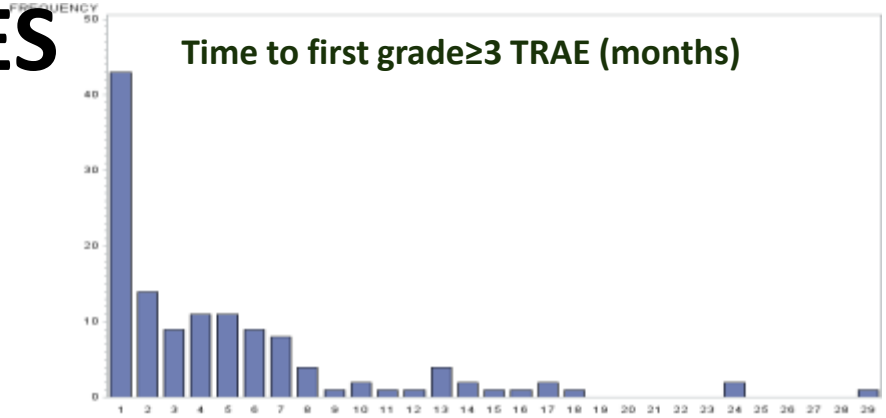
SOC	N=720	
General disorders Asthenia/Fatigue	25	(3.5%)
Gastrointestinal disorders	16	(2.2%)
Metabolic disorder Hyperglycemia/Dyskaliema/Dysnatremia	15	(2.1%)
Musculoskeletal and connective tissue disorders	12	(1.7%)
Respiratory, thoracic and mediastinal disorders	10	(1.4%)
Renal and urinary disorders	10	(1.4%)
Blood disorders	9	(1.3%)
Skin reaction	8	(1.1%)
Infections	7	(1.0%)
Hepatobiliary disorders	7	(1.0%)
Nervous system disorders	5	(0.7%)
Endocrine disorders	4	(0.6%)
Cardiac disorders	3	(0.4%)
Psychiatric disorders	2	(0.3%)
Uveitis	2	(0.3%)
Allergic reaction	1	(0.1%)

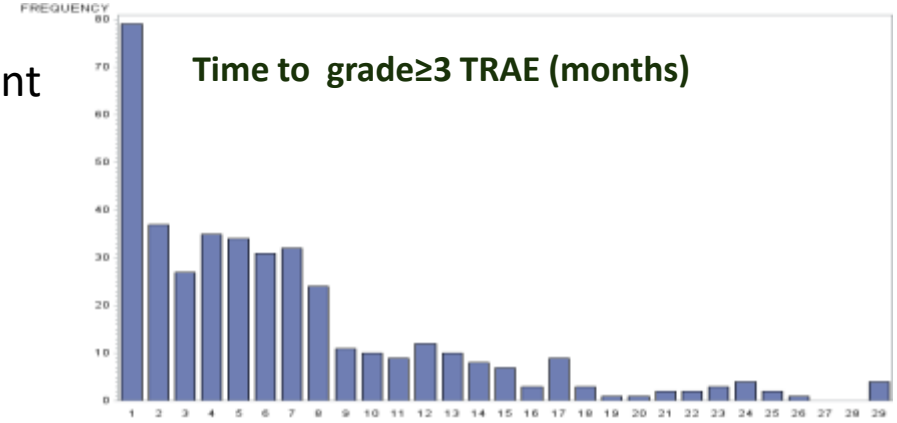
Safety - Grade 3-5 TRAES

Among the 129 patients with grade ≥ 3 TRAE,

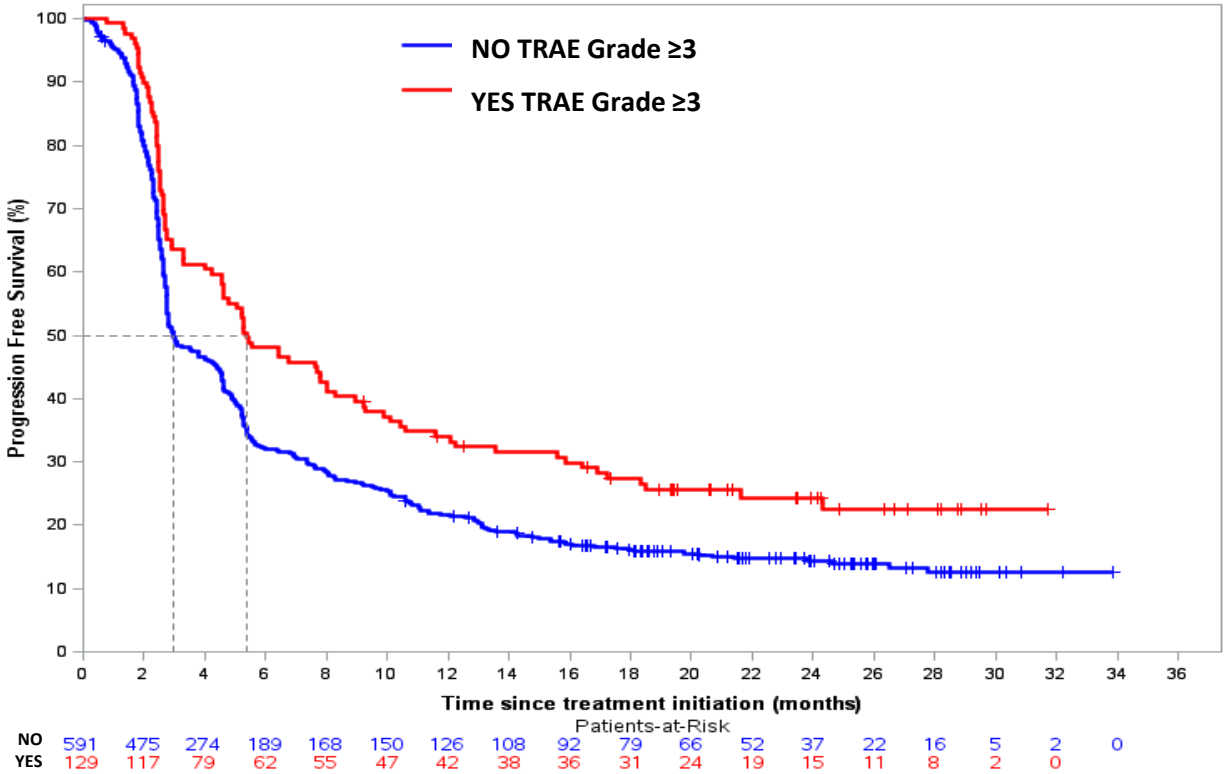
median time to first grade ≥ 3 TRAE was 3.3 mo (0-29.9)

mean number of grade ≥ 3 TRAE was 3.1/ patient





TRAE grade ≥3 is associated with PFS



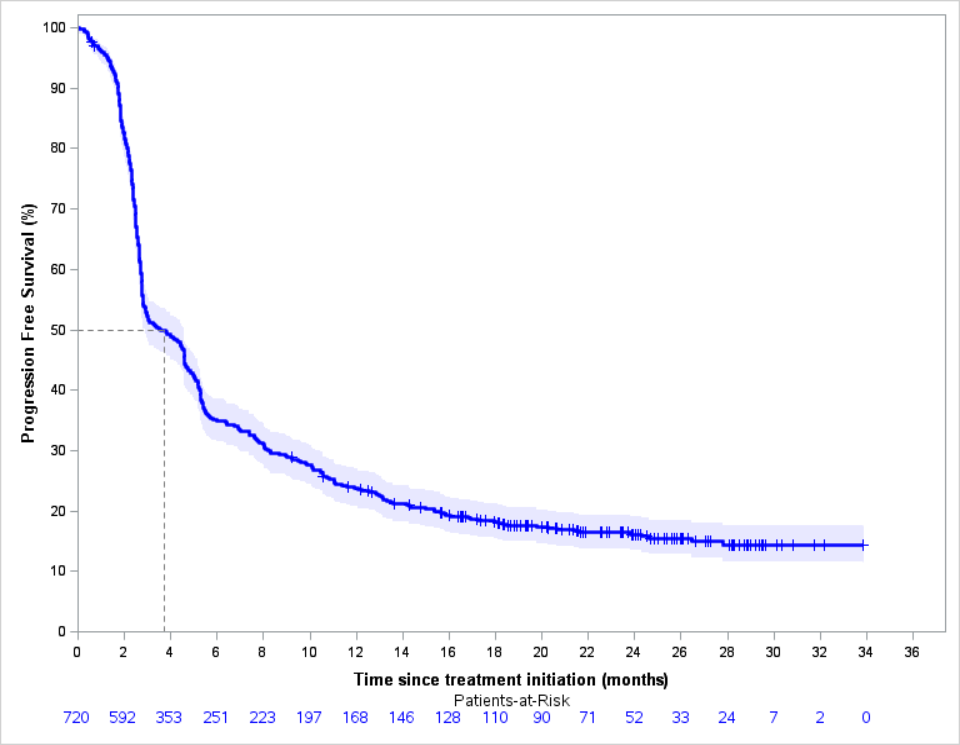
TRAE grade ≥ 3	Median PFS	HR (95% CI)
No	3.0 (2.8-4.1)	0.69 [0.56-0.86]
Yes	5.4 (4.6-8.0)	

Activity (1) ORR – RECIST1.1

Outcome	N = 720
Confirmed ORR, % (95% CI)	**144 (21%)**
BOR, %	
Complete response	9 (1.3%)
Partial response	135 (19.7%)
Stable disease	214 (31.1%)
Progressive disease	329 (47.9%)
Unable to determine/not reported	7

47.0% patients received treatment beyond progression

Activity (2) PFS



Median PFS : 3.7 months CI95% [2.9– 4.6]

6 mo-PFS rate: 35.0% [31.5;38.5]
12 mo-PFS rate: 23.8 % [20.7;27.0]

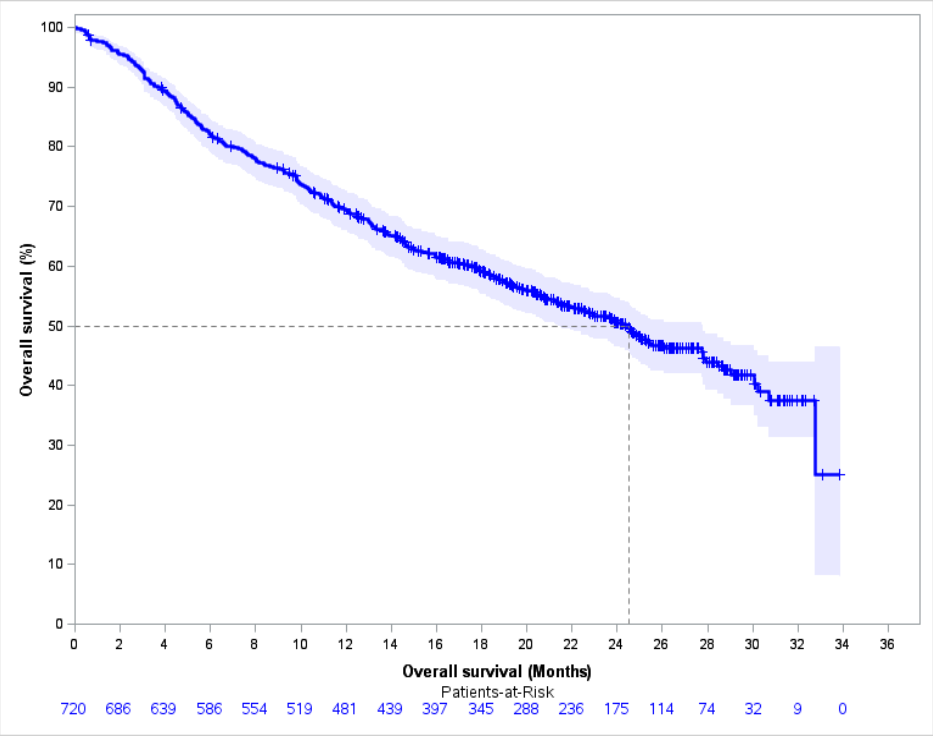
Time to subsequent systemic therapy

- Out of 720 patients, 381 received subsequent therapy (59%) and 155 died without subsequent treatment (22%)

- Median time to subsequent therapy was 8.1mo (7.3-9.0)

subsequent therapy	N=720	
Cabozantinib	198	(27.5%)
Axitinib	93	(12.9%)
Everolimus	34	(4.7%)
Sorafenib	10	(1.4%)
Others	46	(6.4%)

Activity (3) OS



Median OS : 24.5 months CI95% [21.4– 27.8]

6 mo-OS rate: 82.0% [79.0;84.6]
12 mo-OS rate: 69.4% [65.9;72.7]

**Median Follow up : 23.9 months $CI_{95\%}$[23.0;24.6]*

Subgroup analysis (univariate analysis)

Subgroup		Median PFS	HR (95% CI)	Median OS	HR (95% CI)
ECOG	**0-1**	4.3 (3.0-4.6)	1.22 (0.97-1.53) p=0.0892	26.1 (24.1-29.1)	2.11 (1.62-2.76) p<.0001
	2	2.7 (2.2-4.4)		11.2 (6.0-15.9)	

Subgroup analysis (univariate analysis)

Subgroup		Median PFS	HR (95% CI)	Median OS	HR (95% CI)
ECOG	**0-1**	4.3 (3.0-4.6)	1.22 (0.97-1.53) p=0.0892	26.1 (24.1-29.1)	2.11 (1.62-2.76) p<.0001
	2	2.7 (2.2-4.4)		11.2 (6.0-15.9)	
Nb of prior lines	**1-2**	3.3 (2.8-4.5)	1.11 (0.92-1.34) p=0.2632	25.0 (22.8-28.7)	1.14 (0.90-1.46) p= 0.2712
	>2	4.5 (2.8-5.1)		20.4 (17.5-25.5)	

Subgroup analysis (univariate analysis)

Subgroup		Median PFS	HR (95% CI)	Median OS	HR (95% CI)
ECOG	**0-1**	4.3 (3.0-4.6)	1.22 (0.97-1.53) p=0.0892	26.1 (24.1-29.1)	2.11 (1.62-2.76) p<.0001
	2	2.7 (2.2-4.4)		11.2 (6.0-15.9)	
Nb of prior lines	**1-2**	3.3 (2.8-4.5)	1.11 (0.92-1.34) p=0.2632	25.0 (22.8-28.7)	1.14 (0.90-1.46) p= 0.2712
	>2	4.5 (2.8-5.1)		20.4 (17.5-25.5)	
Prior everolimus	**no**	3.8 (2.9-4.6)	1.13 (0.93-1.37) p=0.2159	26.1 (23.9-30.1)	1.43 (1.13-1.81) p=0.0027
	yes	3.0 (2.7-4.6)		19.0 (14.6-21.5)	

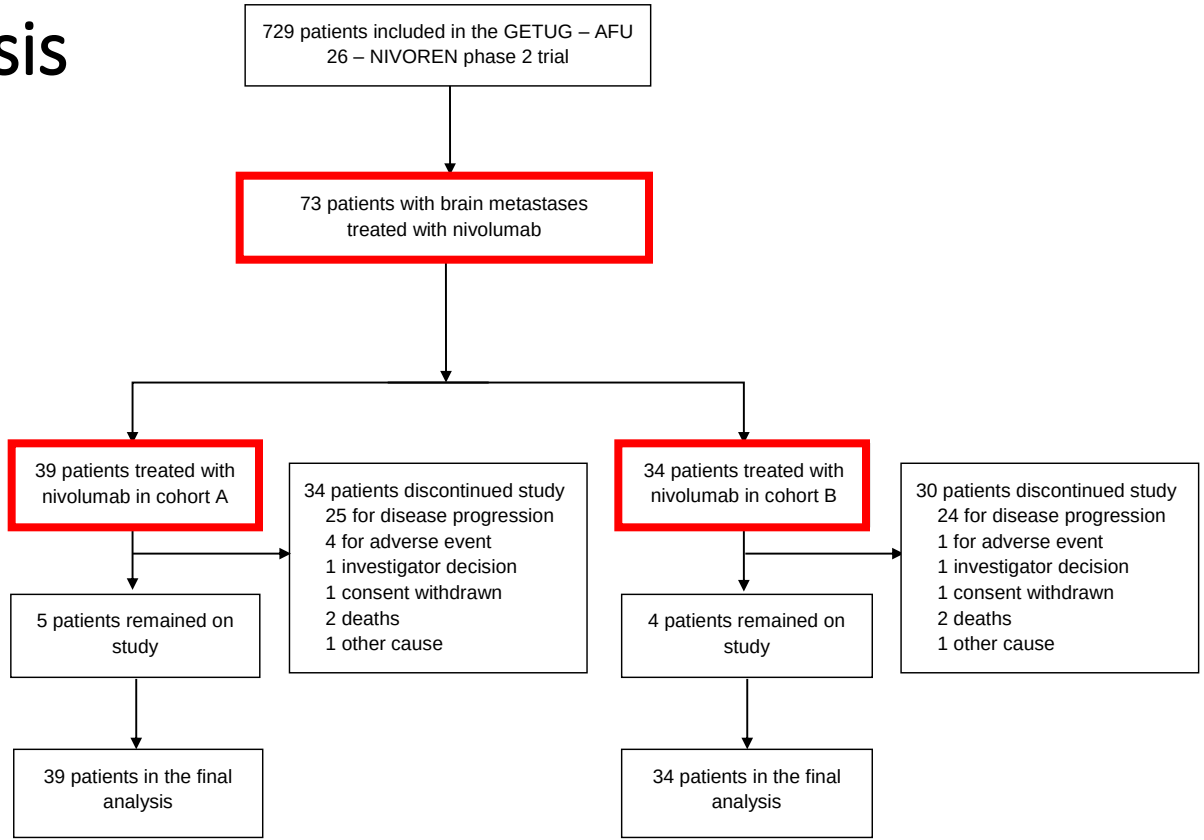
Subgroup analysis (univariate analysis)

Subgroup		Median PFS	HR (95% CI)	Median OS	HR (95% CI)
ECOG	**0-1**	4.3 (3.0-4.6)	1.22 (0.97-1.53) p=0.0892	26.1 (24.1-29.1)	2.11 (1.62-2.76) p<.0001
	2	2.7 (2.2-4.4)		11.2 (6.0-15.9)	
Nb of prior lines	**1-2**	3.3 (2.8-4.5)	1.11 (0.92-1.34) p=0.2632	25.0 (22.8-28.7)	1.14 (0.90-1.46) p= 0.2712
	>2	4.5 (2.8-5.1)		20.4 (17.5-25.5)	
Prior everolimus	**no**	3.8 (2.9-4.6)	1.13 (0.93-1.37) p=0.2159	26.1 (23.9-30.1)	1.43 (1.13-1.81) p=0.0027
	yes	3.0 (2.7-4.6)		19.0 (14.6-21.5)	
GFR (ml/min)	**≥60**	3.3 (2.8-4.6)	1.01 (0.85-1.19) p=0.9426	25.3 (23.6-30.7)	1.26 (1.01-1.56) p=0.0367
	<60	3.6 (2.8-5.0)		19.8 (17.2-24.8)	

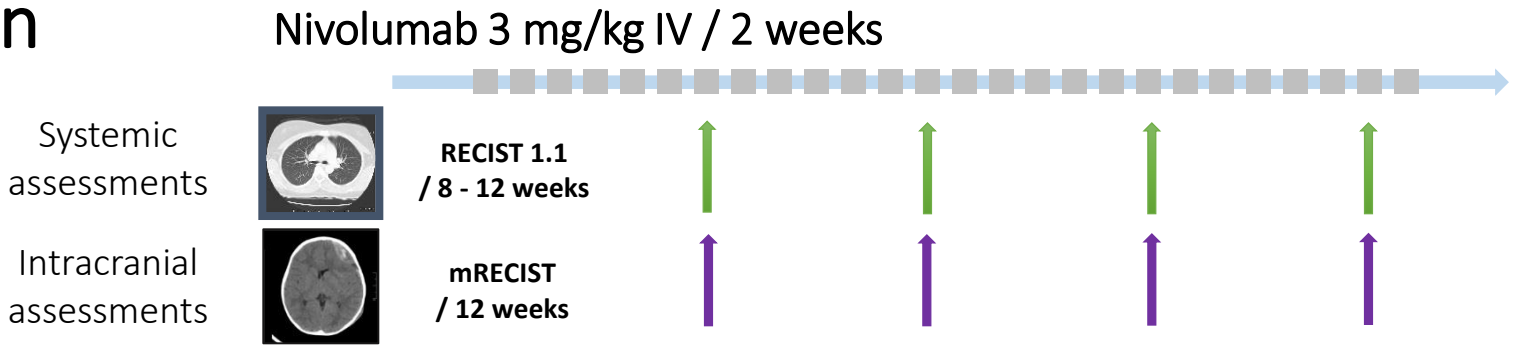
Subgroup analysis (univariate analysis)

Subgroup		Median PFS	HR (95% CI)	Median OS	HR (95% CI)
ECOG	**0-1**	4.3 (3.0-4.6)	1.22 (0.97-1.53) p=0.0892	26.1 (24.1-29.1)	2.11 (1.62-2.76) p<.0001
	2	2.7 (2.2-4.4)		11.2 (6.0-15.9)	
Nb of prior lines	**1-2**	3.3 (2.8-4.5)	1.11 (0.92-1.34) p=0.2632	25.0 (22.8-28.7)	1.14 (0.90-1.46) p= 0.2712
	>2	4.5 (2.8-5.1)		20.4 (17.5-25.5)	
Prior everolimus	**no**	3.8 (2.9-4.6)	1.13 (0.93-1.37) p=0.2159	26.1 (23.9-30.1)	1.43 (1.13-1.81) p=0.0027
	yes	3.0 (2.7-4.6)		19.0 (14.6-21.5)	
GFR (ml/min)	**≥60**	3.3 (2.8-4.6)	1.01 (0.85-1.19) p=0.9426	25.3 (23.6-30.7)	1.26 (1.01-1.56) p=0.0367
	<60	3.6 (2.8-5.0)		19.8 (17.2-24.8)	
Brain Metastasis	**No**	4.4 (3.0-4.8)	1.42 (1.12-1.81) p=0.0039	25.0 (22.4-29.1)	1.30 (0.95-1.78) p=0.0988
	Yes	2.8 (2.5-4.2)		19.0 (14.2-27.7)	

Brain mets analysis



Design

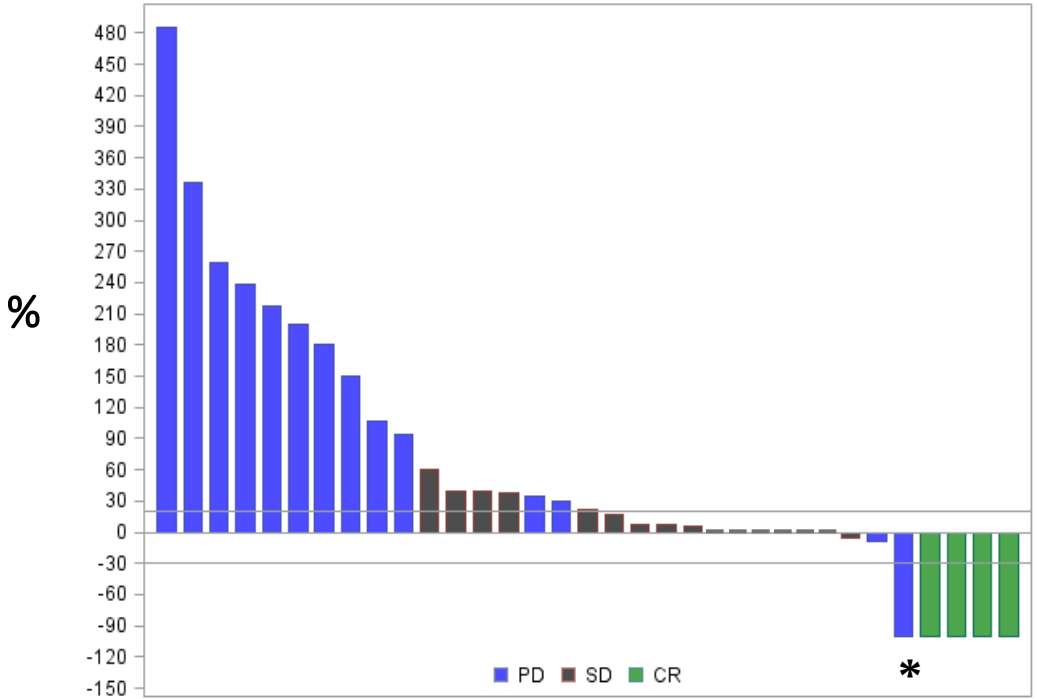


Main endpoint: Intracranial response rate in cohort A

Secondary endpoints

- Extracranial response
- Intracranial and extracranial Progression-Free Survival
- Overall Survival
- Safety (CTCAE v4.0)
- Specific CNS criteria: CNS symptoms, use of corticosteroids, brain focal therapy

Brain response in untreated patients



* *Occurrence of new brain lesion*

Brain response in untreated patients

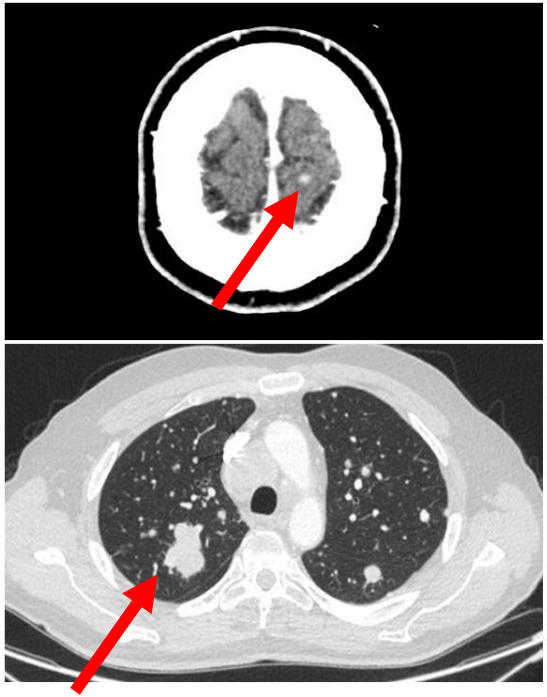
Cohort A
Untreated brain metastases
N = 39

	Intracranial	Extracranial
Best response		
Complete Response	4 (12%)	0 (0%)
Partial Response	0 (0%)	7 (21%)
Stable disease	13 (38%)	10 (30%)
Progressive disease	17 (50%)	16 (49%)
Missing	5	6
Overall response rate, % (95% CI)	4 (11.8%; 3.3-27.5)	7 (21.2%; 9.0-38.9)
Median progression-free survival, months (95% CI)	2.7 (2.3-4.6)	2.8 (2.2-4.6)
6-month progression-free survival rate, % (95% CI)	23.8% (11.1%-39.2%)	27.8% (14.8%-42.3%)
12-month overall survival rate, % (95% CI)	66.7% (49.6%-79.1%)	

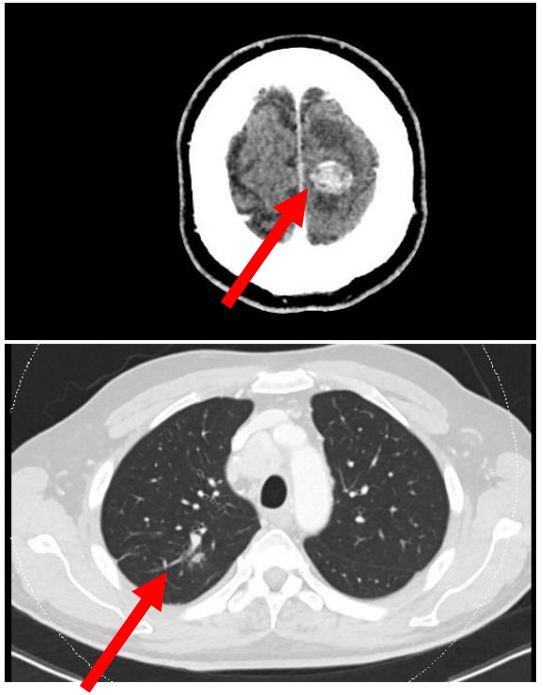
Brain response in untreated patients

	N	Missing	Best intracranial response CR	SD	PD
ECOG PS					
Missing		1	0	0	1
0,1	33	3	3 (10%)	12 (40%)	15 (50%)
2,3	4	1	1 (33%)	1 (33%)	1 (33%)
Number of brain metastases					
1	26	3	4 (17%)	10 (43%)	9 (39%)
>1	13	2	0 (0%)	3 (27%)	8 (73%)
Furhman grade					
Missing		0	2	0	1
I/II	13	1	2 (17%)	6 (50%)	4 (33%)
III/IV	23	4	0 (0%)	7 (37%)	12 (63%)
Previous lines of systemic therapy					
1-2	15	3	1 (8%)	5 (42%)	6 (50%)
≥ 2	24	2	3 (14%)	8 (36%)	11 (50%)
IMDC risk groups					
Missing		0	0	0	1
Good or Intermediate	25	3	2 (9%)	12 (55%)	8 (36%)
Poor	13	2	2 (18%)	1 (9%)	8 (72%)
Sum of the longest diameter of brain target lesions					
< 10mm	18	3	4 (27%)	5 (33%)	6 (40%)
> 10mm	21	2	0 (0%)	8 (42%)	11 (58%)

Brain and extracranial response in untreated patients

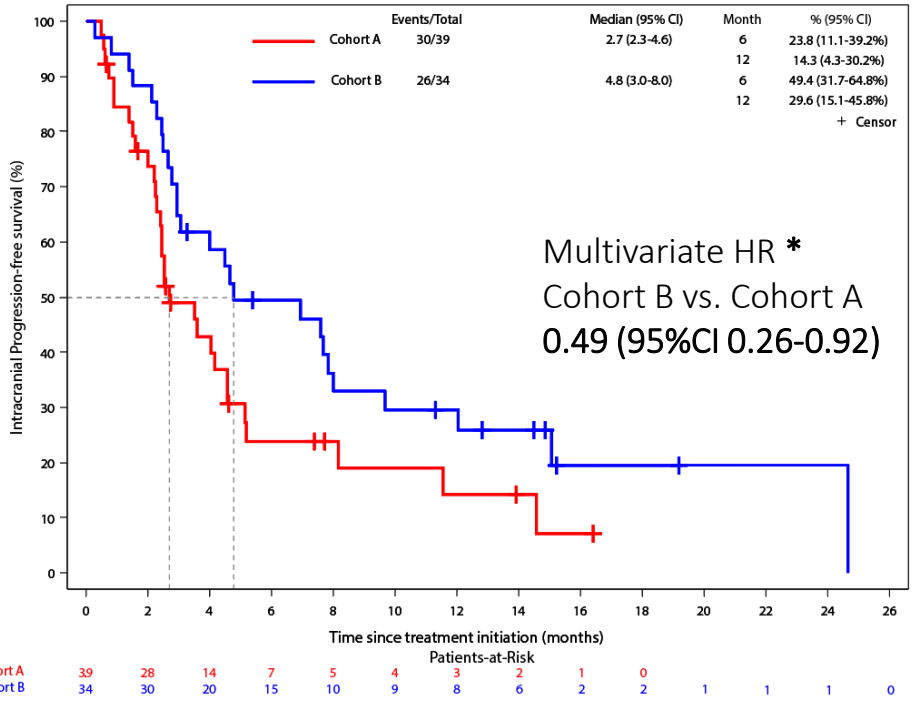


Baseline



Month 2

Brain progression-free survival in cohorts A and B



Progression with new brain metastases

14/30 (47%) in cohort A
9/26 (35%) in cohort B

***** Variables:

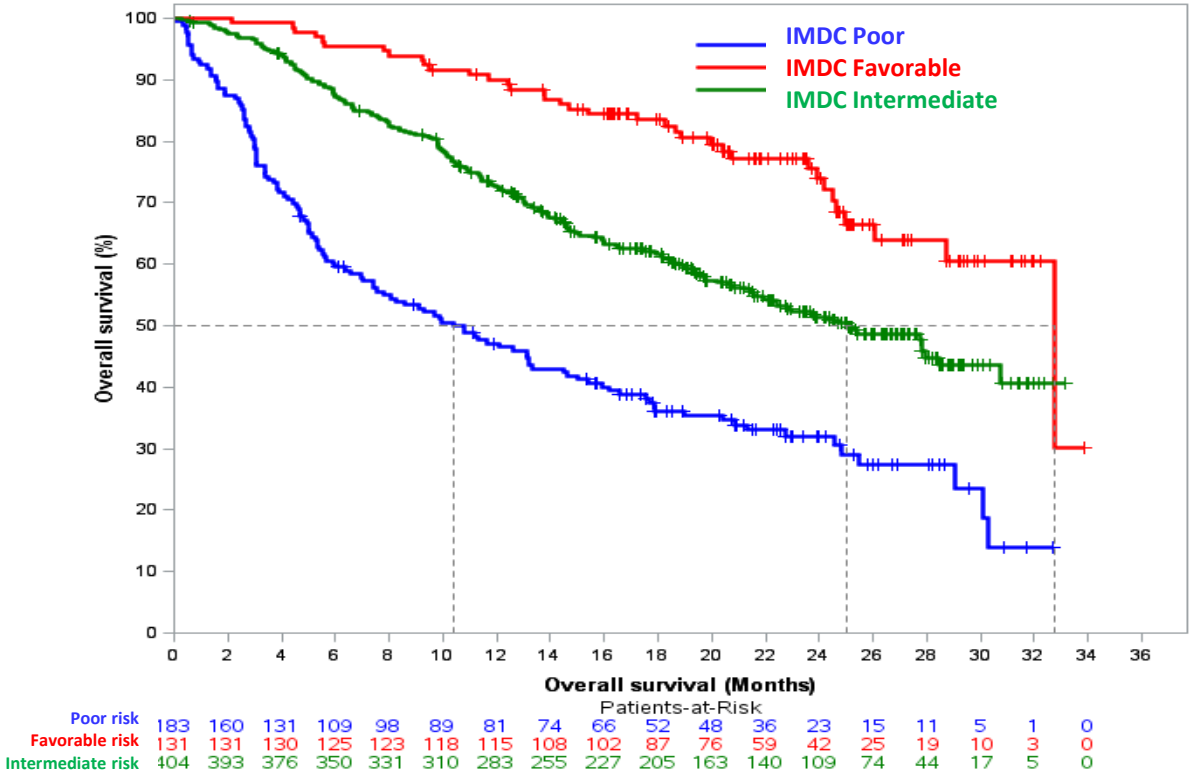
ECOG (0-1 vs. 2+)
Number Of brain lesions(1 vs. >1)
Furhman grade (1-2 vs. 3-4)
Prior systemic therapies(1 vs. >1)
IMDC (favourable/intermediate vs. Poor)

Lessons from the GETUG - AFU 26 – NIVOREN trial

Limited intracranial activity of nivolumab in patients with untreated brain metastases from ccRCC

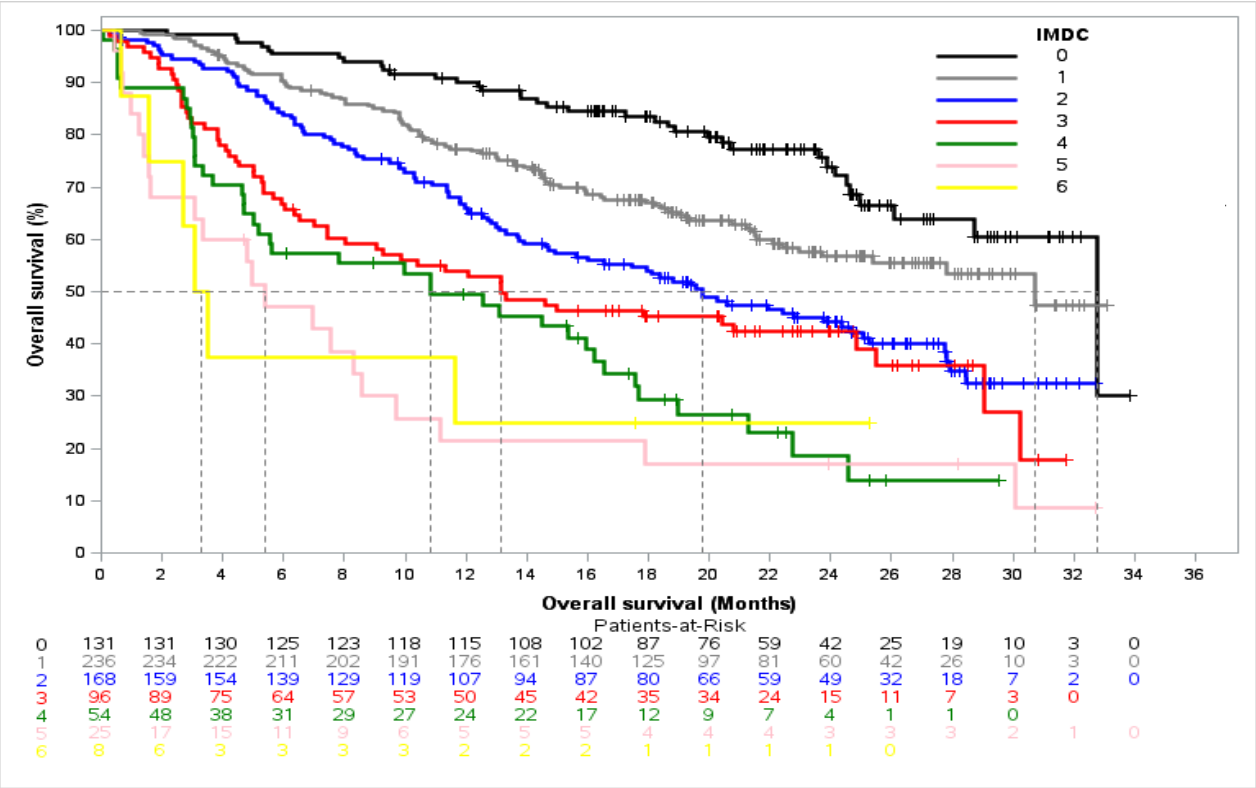
Objective response 12%, only in unique lesions < 10 mm
73% PD as best response in case of multiple metastases

OS according to IMDC prognostic risk groups



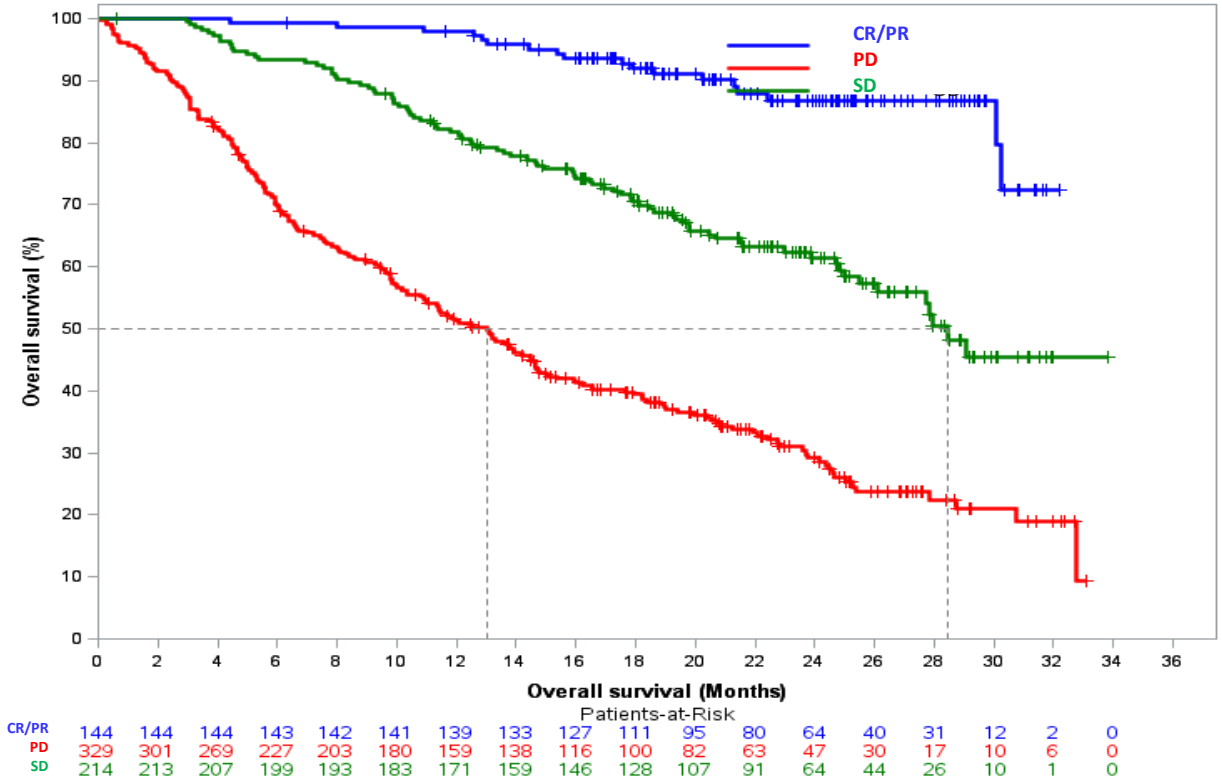
IMDC	Median OS	HR (95% CI)
Favorable	32.8 (28.7-NE)	-
Intermed.	25.0 (21.5-30.7)	2.04 (1.43-2.92)
Poor	10.4 (7.0-14.5)	4.36 (3.00-6.33)

OS according to IMDC risk factor number



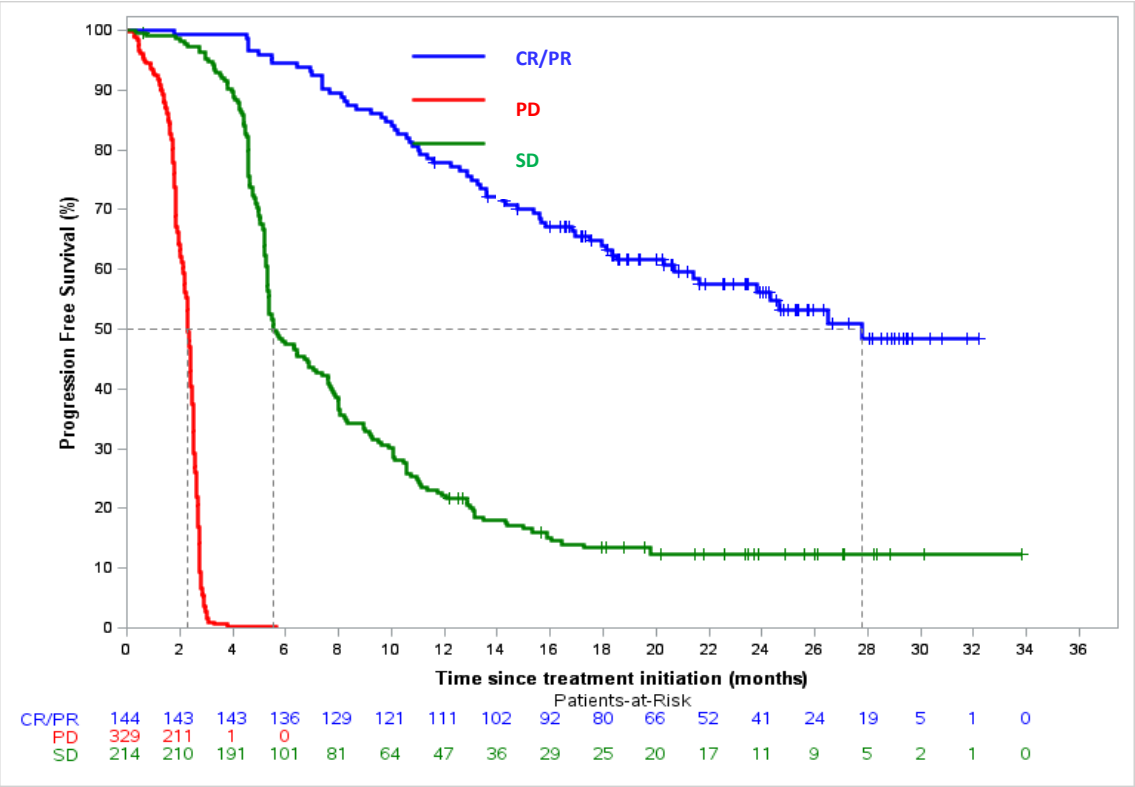
IMDC	Median OS	HR (95% CI)
0	32.8 (28.7-NE)	1
1	30.7 (23.7-NE)	1.67 (1.14-2.46)
2	19.8 (14.7-25.0)	2.62 (1.78-3.84)
3	13.2 (7.4-25.5)	3.39 (2.24-5.15)
4	10.8 (5.0-16.2)	5.14 (3.27-8.09)
5	5.4 (1.6-8.6)	7.29 (4.24-12.52)
6	3.3 (0.7-NE)	7.07 (2.97-16.82)

Best response is associated with OS



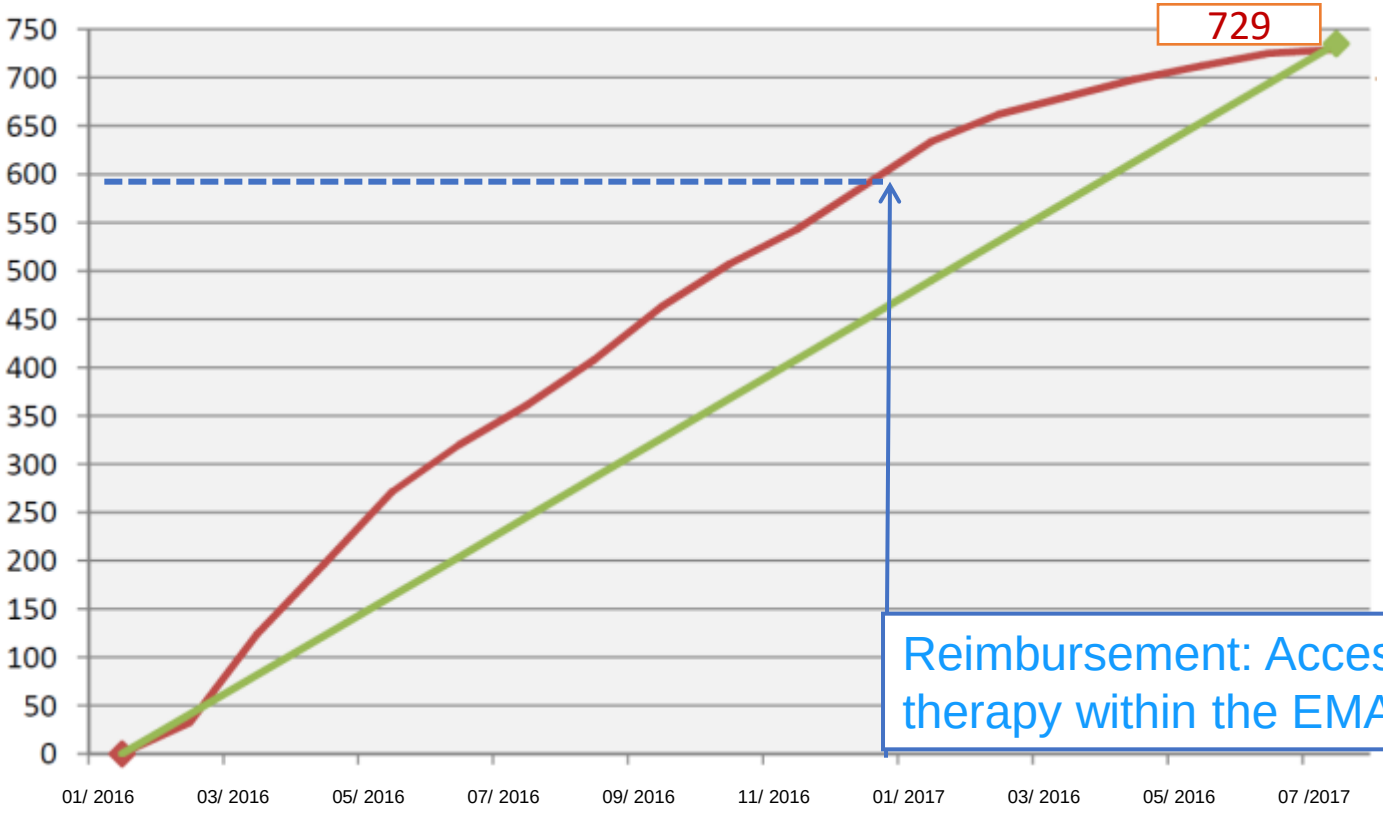
Best response	Median OS	HR (95% CI)
CR/PR	NE (30.3-NE)	1
SD	28.4 (25.5-NE)	3.77 (2.26-6.26)
PD	13.0 (10.3-14.6)	9.95 (6.14-16.10)

Best response is associated with PFS



Best response	Median PFS
CR/PR	27.8 (21.4-NE)
SD	5.6 (5.3-7.0)
PD	2.3 (2.2-2.4)

New agent: an urgent medical need



Summary of the findings

	CheckMate 025	GETUG- AFU 26 NIVOREN
n	406	**720**
Median FUp	14 mo (minimum Fup)	**23.9 mo**
Median PFS	4.6 mo	**3.7 mo**
Median OS	25.0 mo	**24.5 mo**
ORR SD PD	25% 34% 35%	**21.0%** **31.1%** **47.9%**
Ttt beyond progression	44%	**47.0%**
Grade ≥3 TRAEs	19%	**17.9%**

Presented by: Laurence Albiges, MD PhD

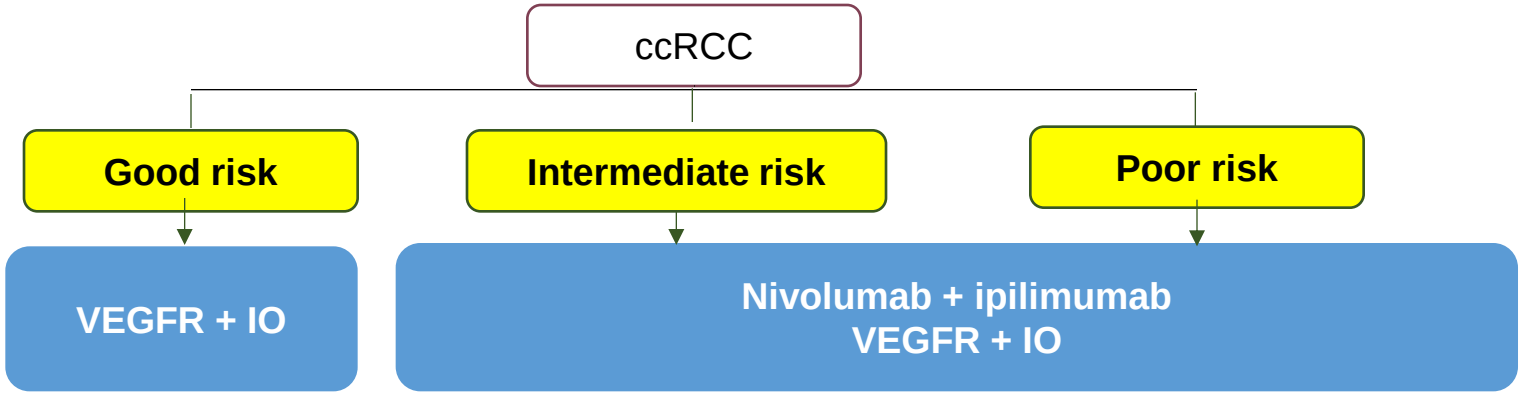
Conclusions

- GETUG-AFU 26 NIVOREN is the largest prospective real world setting study of nivolumab in mRCC
- Nivolumab safety and efficacy in a “real world” prospective study are similar to the pivotal study
- Grade ≥ 3 TRAE
  - Occurred in 17.9%
  - With median time to first event 3.3 mo
  - Is multiple (mean 3.1/pt)
  - was associated with longer PFS

Conclusions

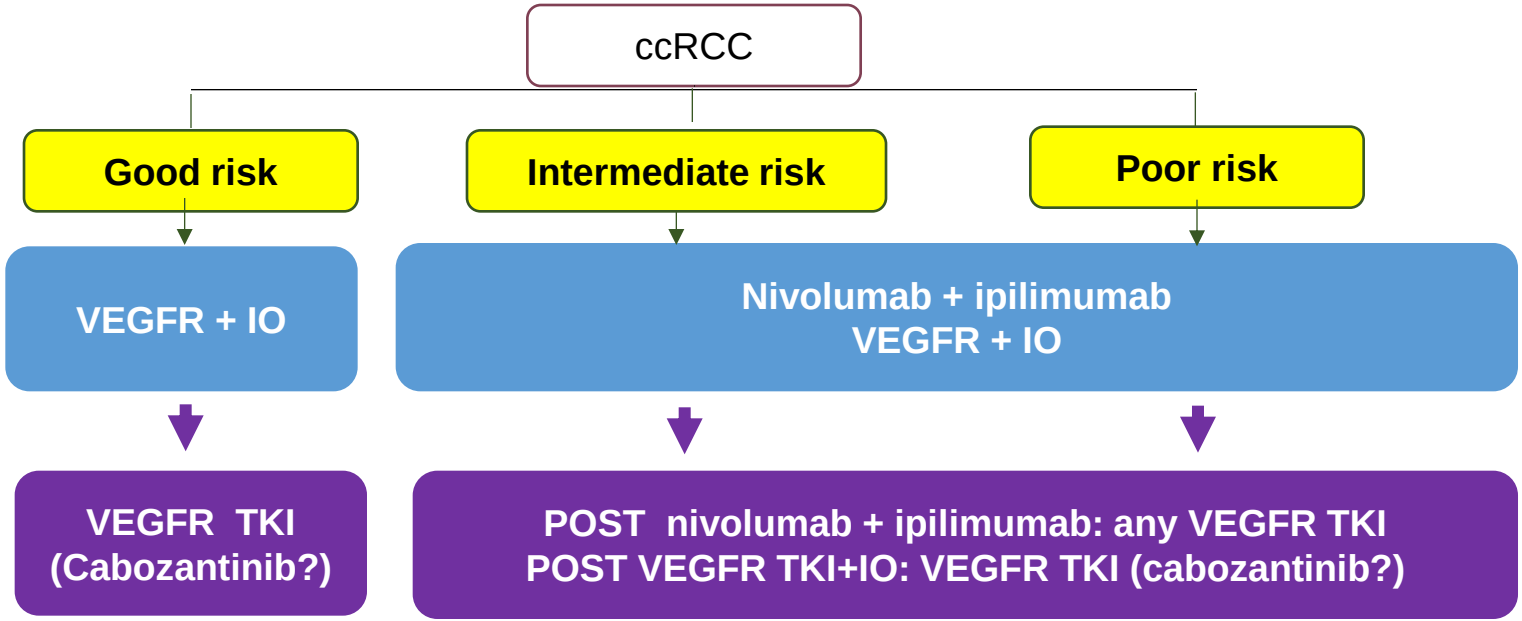
- 59% of patients heavily pretreated could received subsequent TTT after nivolumab
- IMDC classification and risk factor number are highly prognosis (predictive?) in patients treated with nivolumab
- RECIST investigator assessed best response correlates with overall survival
- Many open questions:
  - How long to treat CR
  - Challenge of Brain Metastasis
  - How to rescue upfront or secondary resistance?
- Translational program is ongoing

New algorithm, new sequence?



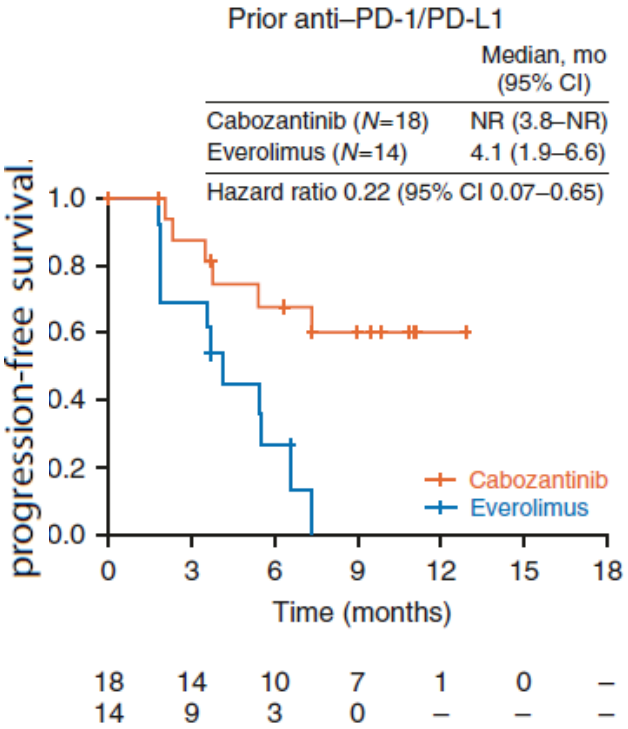
Proposed algorithm , adapted from ESMO guidelines recommendation

New algorithm, new sequence?

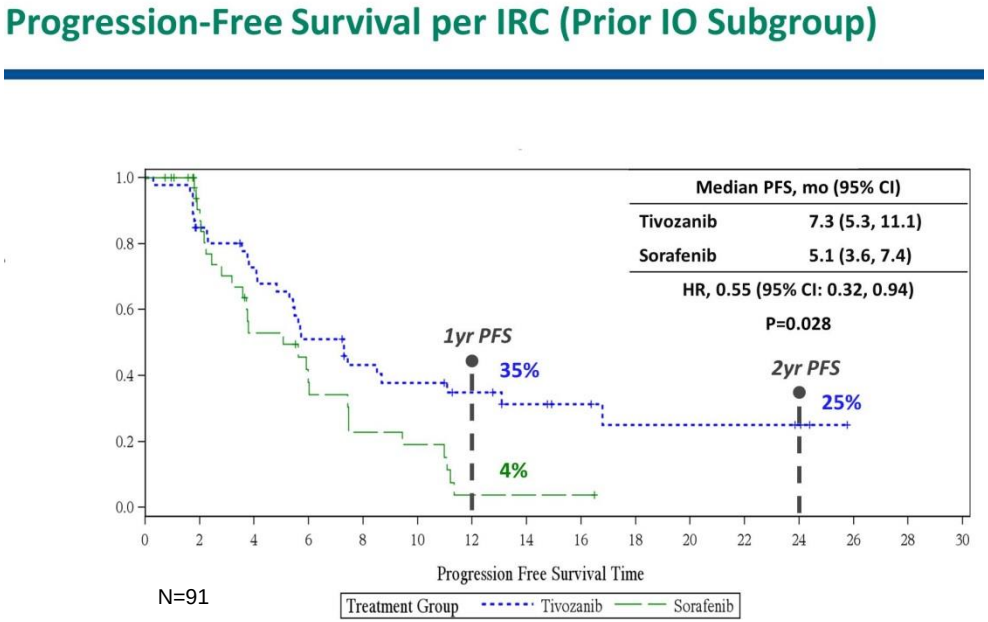


Proposed algorithm

Post IO : limited RCT data available



Meteor study Powles et al. BJC 2018



TIVO-3 study . Rini et al. ASCO GU 2019

European Journal of Cancer 108 (2019) 33–40

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

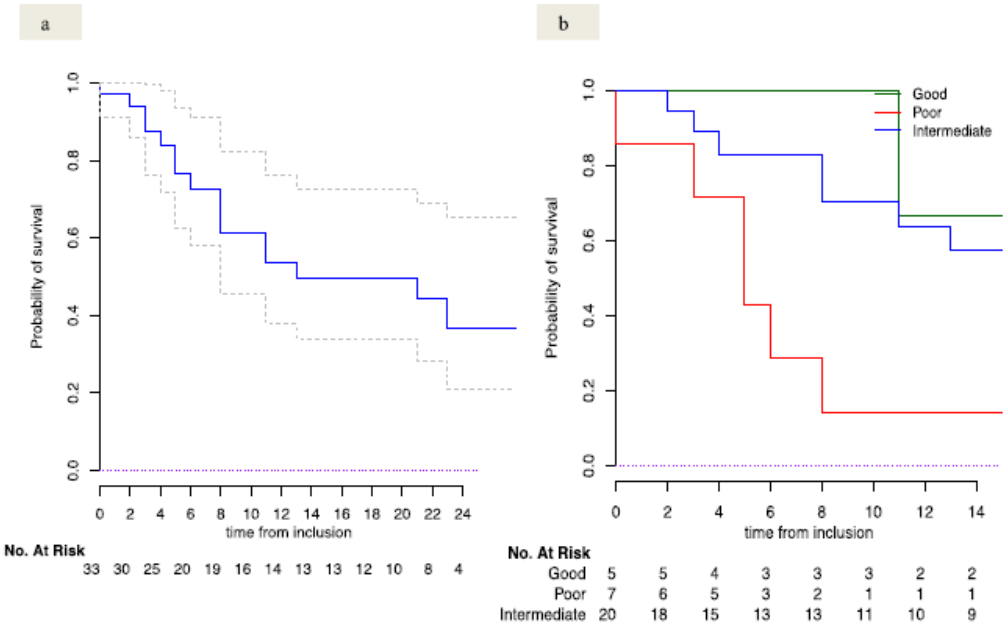
Original Research

Second-line targeted therapies after nivolumab-ipilimumab failure in metastatic renal cell carcinoma

ORR 36%
Median PFS: 8 months
OS: 54% at 12 months

VEGFR TKI

- sunitinib (17)
- axitinib (8)
- pazopanib (6)
- cabozantinib (2)



Auvray et al EJC 2019

Poster #584
Patterns of First-line Combo Therapy: 2nd line Outcomes

Table 3: Outcomes for 2L VEGF-TKI Monotherapy

	PD(L)1-VEGF (N=15)	Ipi-Nivo (N=20)	P-value
2L Response Rate	13%	45%	0.07
2L Time to Treatment Failure (months)	5.5 (2.2 – 10.2)	5.4 (3.1 – 8.3)	0.80

Summary

- Real world data answer day to day question!
- Little is known about the optimal sequence
- Changes in First line will require to define the best strategy in
  - Nivolumab-ipilimumab failure
  - VEGFR TKI- IO (axitinib-pembrolizumab) failure

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Gustave Roussy GU Group

laurence.albiges@igr.fr